CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040103

Trade Name : BENZTROPINE MESYLATE TABLETS

Generic Name: Benztropine Mesylate Tablets

Sponsor : Rosemont Pharmaceutical Corp

Approval Date: December 12, 1996

ANDA 40-103

DEC 12 1996

Rosemont Pharmaceutical Corporation
Attention: Donald H. Waters, Ph.D.
301 South Cherokee Street
Denver, CO 80223

Dear Sir:

This is in reference to your abbreviated new drug application dated April 29, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Benztropine Mesylate Tablets USP, 0.5 mg, 1 mg and 2 mg.

Reference is also made to your amendment dated November 13, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Benztropine Mesylate Tablets USP, 0.5 mg, 1 mg and 2 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Cogentin® (Benztropine Mesylate Tablets, 0.5 mg, 1 mg and 2 mg of Merck Sharp & Dohme). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

12/12/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-103
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-8/PSavino
HFD-610/JPhillips

Endorsements:
HFD-625/SSherken/12/2/96 12/5/96
HFD-617/SO'Keefe/12/3/96 12/5/96
HFD-625/MSmela/12/3/96 12/5/96
HFD-613/CHolquist/12/3/96 12/5/96
HFD-613/JGrace/12/4/96 12/5/96
X:\NEW\FIRMSNZ\ROSEMONT\LTRS&REV\40103.APL
F/t by: GP/12/4/96
APPROVAL

12/10/96

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 40-103

3. NAME AND ADDRESS OF APPLICANT

Rosemont Pharmaceutical Corp.
Denver, CO 80223

4. LEGAL BASIS FOR ANDA SUBMISSIONS

505(j), 21 CFR 314.94(d)(5) & 314.440

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Benztropine Mesylate USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES

DOA 4/29/94; Corres 5/24/94; Corres 6/29/94; NA 10/26/94; Bio Letter 11/23/94; Corres (Bio) 10/24/94; Corres (Bio) 12/1/94; Bio letter 3/10/95; Corres 4/19/95; Amend (major) 5/11/95; Corres (Bio) 6/9/95; NA 11/27/95; Amend (minor) 1/15/96; NA 7/5/96; Amend 8/2/96; NA (Minor) 8/16/96; Amend 8/29/96; NA (minor) 10/17/96; *Amend (minor) 11/13/96

* reviewed amendment

10. PHARMACOLOGICAL CATEGORY

Anti-Parkinsonism
Control of extrapyramidal disorders

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

14. POTENCY

1. Compressed ¼" diameter white, flat beveled edged, single scored & debossed 832 & BM05 & one side plain tablets.	0.5 mg
2. Compressed white, 0.231" x 0.420" oval single scored & debossed 832 & BM1 & one side plain tablets.	1 mg
3. Compressed 9/32" diameter white, flat beveled edged, single scored & debossed 832 & BM2 & one side plain tablets.	2 mg

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Review of for Benztropine Sulfate USP was reviewed by Mr. Sherken on 11/27/96. n now adequate.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA is approvable.

Bio is acceptable.

Chemistry, manufacturing, testing of Benztropine Mesylate Tablets USP and Benztropine Mesylate USP are now satisfactory.

Labeling is acceptable.

EER found acceptable on 8/9/96.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken November 27, 1996

Each Tablet Contains:
Benztropine Mesylate, USP 0.5 mg
Usual Adult Dosage: For parkinsonism, 1 to 2 mg daily. For drug induced extrapyramidal disorders, 1 to 4 mg once or twice a day. See accompanying insert.
This is a bulk package and not intended for dispensing.
Dispense in well-closed containers as defined in the USP.
Keep this and all drugs out of the reach of children.
Store at controlled room temperature 15°-30°C (59°-86°F).

5001080 1000

Lot No.:
Exp.:

NDC 0832-1080-10

Benztropine Mesylate Tablets, USP

0.5 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

ROSEMONT

Mfd. by: Rosemont Pharmaceutical Corp.
Denver, Colorado 80223
50-01080-10-00 Iss. 1-95

3 0832-1080-10 8

Each Tablet Contains:
Benztropine Mesylate, USP 0.5 mg
Usual Adult Dosage: For parkinsonism, 1 to 2 mg daily. For drug induced extrapyramidal disorders, 1 to 4 mg once or twice a day. See accompanying insert.
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Denver, Colorado 80223
50-01080-10-00 Iss. 1-95

3 0832-1080-10 8

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Lot No.:
Exp.:

NDC 0832-1080-10

Benztropine Mesylate Tablets, USP

0.5 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

ROSEMONT

Mfd. by: Rosemont Pharmaceutical Corp.
Denver, Colorado 80223
50-01080-10-00 Iss. 1-95

3 0832-1080-10 8

Benztropine Mesylate Tablets, USP 0.5 mg, 1 mg, 2 mg — *ANDA #40-103*
Rosemont Pharmaceutical Corporation
Major Amendment Response -- 10/26/94

Lot No.:
Exp.:

Each Tablet Contains:
Benztropine Mesylate, USP 0.5 mg
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This is a bulk package and not intended for dispensing.
Dispense in well-closed containers as defined in the USP.
Keep this and all drugs out of the reach of children.
Store at controlled room temperature 15°-30°C (59°-86°F)

50010800000

NDC 0832-1080-00
Benztropine Mesylate Tablets, USP
0.5 mg
Caution: Federal law prohibits dispensing without prescription.
100 Tablets
ROSEMONT

Mfd. by: Rosemont Pharmaceutical Corp.
Denver, Colorado 80223
50-01080-00-00 Iss. 1-95

N 3 0832-1080-00 6

Lot No.:
Exp.:

Each Tablet Contains:
Benztropine Mesylate, USP 0.5 mg
Usual Adult Dosage: For parkinsonism, 1 to 2 mg daily. For drug induced extrapyramidal disorders, 1 to 4 mg once or twice a day. See accompanying insert.
This is a bulk package and not intended for dispensing.
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Store at controlled room temperature 15°-30°C (59°-86°F)

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NDC 0832-1080-00
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0.5 mg
Caution: Federal law prohibits dispensing without prescription.
100 Tablets
ROSEMONT

Mfd. by: Rosemont Pharmaceutical Corp.
Denver, Colorado 80223
50-01080-00-00 Iss. 1-95

N 3 0832-1080-00 6

Lot No.:
Exp.:

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Benztropine Mesylate, USP 0.5 mg
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0.5 mg
Caution: Federal law prohibits dispensing without prescription.
100 Tablets
ROSEMONT

Mfd. by: Rosemont Pharmaceutical Corp.
Denver, Colorado 80223
50-01080-00-00 Iss. 1-95

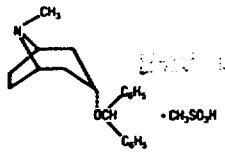
N 3 0832-1080-00 6

BENZTROPINE
MESYLATE TABLETS, USP

ISS. 1-95 15134-00

DESCRIPTION: Benztropine mesylate is a synthetic compound containing structural features found in atropine and diphenhydramine.

It is designated chemically as 8-azabicyclo[3.2.1] octane, 3-(diphenylmethoxy)-,*endo*, methanesulfonate. Its molecular formula is $C_{21}H_{25}NO \cdot CH_4O_3S$, and its structural formula is:



DEC 12

Benztropine mesylate is a crystalline white powder, very soluble in water, and has a molecular weight of 403.54.

Each benztropine mesylate tablet for oral administration contains benztropine mesylate 0.5 mg, 1 mg or 2 mg.

Inactive ingredients: croscarmellose sodium, anhydrous lactose, magnesium stearate, povidone.

CLINICAL PHARMACOLOGY: Benztropine mesylate possesses both anticholinergic and antihistaminic effects, although only the former have been established as therapeutically significant in the management of parkinsonism.

In the isolated guinea pig ileum, the anticholinergic activity of this drug is about equal to that of atropine; however, when administered orally to unanesthetized cats, it is only about half as active as atropine.

In laboratory animals, its antihistaminic activity and duration of action approach those of pyrilamine maleate.

INDICATIONS AND USAGE: For use as an adjunct in the therapy of all forms of parkinsonism.

Useful also in the control of extrapyramidal disorders (except tardive dyskinesia — see PRECAUTIONS) due to neuroleptic drugs (e.g., phenothiazines).

CONTRAINDICATIONS: Hypersensitivity to benztropine mesylate tablets or any component of the tablets.

Because of its atropine-like side effects, this drug is contraindicated in children under three years of age, and should be used with caution in older children.

WARNINGS: Safe use in pregnancy has not been established.

Benztropine mesylate may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

When benztropine mesylate is given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly. Paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including benztropine mesylate, in combination with phenothiazines and/or tricyclic antidepressants.

Since benztropine mesylate contains structural features of atropine, it may produce anhidrosis. For this reason, it should be administered with caution during hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, the alcoholic, those who have central nervous system disease, and those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, the possibility of hyperthermia should be considered. Dosage should be decreased at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired. Severe anhidrosis and fatal hyperthermia have occurred.

PRECAUTIONS:
General
Since benztropine mesylate has cumulative action, continued supervision is advisable. Patients with a tendency to tachycardia and patients with prostatic hypertrophy should be observed closely during treatment.

Dysuria may occur, but rarely becomes a problem. Urinary retention has been reported with benztropine mesylate.

The drug may cause complaints of weakness and inability to move particular muscle groups, especially in large doses. For example, if the neck has been rigid and suddenly relaxes, it may feel weak, causing some concern. In this event, dosage adjustment is required.

Mental confusion and excitement may occur with large doses, or in susceptible patients. Visual hallucinations have been reported occasionally. Furthermore, in the treatment of extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines), in patients with mental disorders, occasionally there may be intensification of mental symptoms. In such cases, antiparkinsonian drugs can precipitate a toxic psychosis. Patients with mental disorders should be kept under careful observation, especially at the beginning of treatment or if dosage is increased.

Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them. Benztropine mesylate is not recommended for use in patients with tardive dyskinesia.

The physician should be aware of the possible occurrence of glaucoma. Although the drug does not appear to have any adverse effect on simple glaucoma, it probably should not be used in angle-closure glaucoma.

ADVERSE REACTIONS: The adverse reactions below, most of which are anticholinergic in nature, have been reported and within each category are listed in order of decreasing severity.
Cardiovascular
Tachycardia.
Digestive
Constipation, dry mouth, nausea, vomiting.

If dry mouth is so severe that there is difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue the drug temporarily.

Slight reduction in dosage may control nausea and still give sufficient relief of symptoms. Vomiting may be controlled by temporary discontinuation, followed by resumption at a lower dosage.

Nervous System
Toxic psychosis, including confusion, disorientation, memory impairment, visual hallucinations; exacerbation of pre-existing psychotic symptoms; nervousness; depression; listlessness; numbness of fingers.

Special Senses
Blurred vision, dilated pupils.

Urogenital
Urinary retention, dysuria.

Metabolic/Immune or Skin
Occasionally, an allergic reaction, e.g., skin rash, develops. If this can not be controlled by dosage reduction, the medication should be discontinued.

DOSAGE AND ADMINISTRATION: Benztropine mesylate tablets should be used when patients are able to take oral medication.

The injection is especially useful for psychotic patients with acute dystonic reactions or other reactions that make oral medication difficult or impossible. It is recommended also when a more rapid response is desired than can be obtained with the tablets.

Because of cumulative action, therapy should be initiated with a low dose which is increased gradually at five or six-day intervals to the smallest amount necessary for optimal relief. Increases should be made in increments of 0.5 mg, to a maximum of 6 mg, or until optimal results are obtained without excessive adverse reactions.

Postencephalitic and Idiopathic Parkinsonism
The usual daily dose is 1 to 2 mg, with a range of 0.5 to 6 mg orally or parenterally.

As with any agent used in parkinsonism, dosage must be individualized according to age and weight, and the type of parkinsonism being treated. Generally, older patients, and thin patients cannot tolerate large doses. Most patients with postencephalitic parkinsonism need fairly large doses and tolerate them well. Patients with a poor mental outlook are usually poor candidates for therapy.

In idiopathic parkinsonism, therapy may be initiated with a single daily dose of 0.5 to 1 mg at bedtime. In some patients, this will be adequate; in others 4 to 6 mg a day may be required.

In postencephalitic parkinsonism, therapy may be initiated in most patients with 2 mg a day in one or more doses. In highly sensitive patients, therapy may be initiated with 0.5 mg at bedtime, and increased as necessary.

When benztropine mesylate is given concomitantly [illegible] patients should be advised to report gastrointestinal complaints promptly. Paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including benztropine mesylate, in combination with phenothiazines and/or tricyclic antidepressants.

Since benztropine mesylate contains structural features of atropine, it may produce anhidrosis. For this reason, it should be administered with caution during hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, the alcoholic, those who have central nervous system disease, and those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, the possibility of hyperthermia should be considered. Dosage should be decreased at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired. Severe anhidrosis and fatal hyperthermia have occurred.

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Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them. Benztropine mesylate is not recommended for use in patients with tardive dyskinesia.

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Digestive
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If dry mouth is so severe that there is difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue the drug temporarily.

Slight reduction in dosage may control nausea and still give sufficient relief of symptoms. Vomiting may be controlled by temporary discontinuation, followed by resumption at a lower dosage.

Nervous System
Toxic psychosis, including confusion, disorientation, memory impairment, visual hallucinations; exacerbation of pre-existing psychotic symptoms; nervousness; depression; listlessness; numbness of fingers.

Special Senses
Blurred vision, dilated pupils.

Urogenital
Urinary retention, dysuria.

Metabolic/Immune or Skin
Occasionally, an allergic reaction, e.g., skin rash, develops. If this can not be controlled by dosage reduction, the medication should be discontinued.

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The injection is especially useful for psychotic patients with acute dystonic reactions or other reactions that make oral medication difficult or impossible. It is recommended also when a more rapid response is desired than can be obtained with the tablets.

Because of cumulative action, therapy should be initiated with a low dose which is increased gradually at five or six-day intervals to the smallest amount necessary for optimal relief. Increases should be made in increments of 0.5 mg, to a maximum of 6 mg, or until optimal results are obtained without excessive adverse reactions.

Postencephalitic and Idiopathic Parkinsonism
The usual daily dose is 1 to 2 mg, with a range of 0.5 to 6 mg orally or parenterally.

As with any agent used in parkinsonism, dosage must be individualized according to age and weight, and the type of parkinsonism being treated. Generally, older patients, and thin patients cannot tolerate large doses. Most patients with postencephalitic parkinsonism need fairly large doses and tolerate them well. Patients with a poor mental outlook are usually poor candidates for therapy.

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In postencephalitic parkinsonism, therapy may be initiated in most patients with 2 mg a day in one or more doses. In highly sensitive patients, therapy may be initiated with 0.5 mg at bedtime, and increased as necessary.

Some patients experience greatest relief by taking the entire dose at bedtime; others react more favorably to divided doses, two to four times a day. Frequently, one dose a day is sufficient, and divided doses may be unnecessary or undesirable.

The long duration of action of this drug makes it particularly suitable for bedtime medication when its effects may last throughout the night, enabling patients to turn in bed during the night more easily, and to rise in the morning.

When benztropine mesylate is started, do not terminate therapy with other antiparkinsonian agents abruptly. If the other agents are to be reduced or discontinued, it must be done gradually. Many patients obtain greatest relief with combination therapy.

Benztropine mesylate may be used concomitantly with Carbidopa-Levodopa, or with levodopa, in which case periodic dosage adjustment may be required in order to maintain optimum response.

Drug-Induced Extrapyramidal Disorders
In treating extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines), the recommended dosage is 1 to 4 mg once or twice a day orally or parenterally. Dosage must be individualized according to the need of the patient. Some patients require more than recommended; others do not need as much.

In acute dystonic reactions, 1 to 2 mL of the injection usually relieves the condition quickly. After that, the tablets, 1 to 2 mg twice a day, usually prevent recurrence.

When extrapyramidal disorders develop soon after initiation of treatment with neuroleptic drugs (e.g., phenothiazines), they are likely to be transient. One to 2 mg of benztropine mesylate tablets two or three times a day usually provides relief within one or two days. After one or two weeks, the drug should be withdrawn to determine the continued need for it. If such disorders recur, benztropine mesylate can be reinstituted.

Certain drug-induced extrapyramidal disorders that develop slowly may not respond to benztropine mesylate.

OVERDOSAGE:

Manifestations
May be any of those seen in atropine poisoning or antihistamine overdosage: CNS depression, preceded or followed by stimulation; confusion; nervousness; listlessness; intensification of mental symptoms or toxic psychosis in patients with mental illness being treated with neuroleptic drugs (e.g., phenothiazines); hallucinations (especially visual); dizziness; muscle weakness; ataxia; dry mouth; mydriasis; blurred vision; palpitations; tachycardia; elevated blood pressure; nausea; vomiting; dysuria; numbness of fingers; dysphagia; allergic reactions, e.g., skin rash; headache; hot, dry, flushed skin; delirium; coma; shock; convulsions; respiratory arrest; anhidrosis; hyperthermia; glaucoma; constipation.

Treatment
Physostigmine salicylate, 1 to 2 mg, SC or IV, reportedly will reverse symptoms of anticholinergic intoxication (Duvoisin, R.C.; Katz, R.J.; Amer. Med. Ass. *206:* 1963-1965, Nov. 25, 1968). A second injection may be given after 2 hours if required. Otherwise, treatment is symptomatic and supportive. Induce emesis or perform gastric lavage (contraindicated in precomatose, convulsive, or psychotic states). Maintain respiration. A short-acting barbiturate may be used for CNS excitement, but with caution to avoid subsequent depression; supportive care for depression (avoid convulsant stimulants such as picrotoxin, pentylenetetrazol, or bemegride); artificial respiration for severe respiratory depression; a local miotic for mydriasis and cyclopegia; ice bags or other cold applications and alcohol sponges for hyperpyrexia, a vasopressor and fluids for circulatory collapse. Darken room for photophobia.

HOW SUPPLIED: Benztropine Mesylate Tablets USP, for oral use, are supplied in the following forms:

As 0.5 mg: Compressed tablet, white, ¼" diameter, flat beveled edge; one side scored and debossed 832 and BM05, one side plain, in bottles of 100 and 1000.

As 1 mg: Compressed tablet, white, 0.231" × 0.420", oval; one side scored and debossed 832 and BM1, one side plain, in bottles of 100 and 10000.

As 2 mg: Compressed tablet, white, 9/32" diameter, flat beveled edge; one side scored and debossed 832 and BM2, one side plain, in bottles of 100 and 1000.

Store at controlled room temperature 15°-30° C (59°-86° F).

Preserve in well-closed containers as defined in the USP.

Caution
Federal law prohibits dispensing without prescription.

REFERENCES:

Childers, R. T., Jr.: Procyclidine and benztropine methanesulfonate compared in drug induced extrapyramidal reactions, Amer. J. Psychiat. *119:* 462-463, Nov. 1962 (in Clinical Notes).

Doshay, L. J.: Five-year study of benztropine (COGENTIN) methanesulfonate. Outcome in three hundred two cases of paralysis agitans, J. Amer. Med. Ass. *162:* 1031-1034, Nov. 10, 1956.

FDA Drug Bulletin, May 1973.

Gallant, D. M.; Bishop, M. P.; Timmons, E.; Steele, C. A.: A controlled evaluation of trifluperidol: A new potent psychopharmacologic agent, Curr. Therapy, Res. *5:* 463-471, Sept. 1963.

Goldman, D.: Clinical experience with trifluoperazine: Treatment of psychotic states, in "Trifluoperazine, Clinical and Pharmacological Aspects", Philadelphia, Lea & Febiger, 1958, pp. 71-86.

Kiloh, L. G.; Smith, J. S.; Williams, S. E.: Antiparkinson drugs as causal agents in tardive dyskinesia, Med. J. Aust. *2:* 591-593. Sept. 22, 1973.

Kruse, W.: Treatment of drug-induced extrapyramidal symptoms (A comparative study of three antiparkinson agents), Dis. Nerv. Syst. *21:* 79-81, Feb. 1960.

O'Doherty, D.; Forster, F. M.: The use of benztropine sulfonate in the treatment of parkinsonism, Med. Ann. D.C., *22:* 221-223, May 1953. (abst. J. Amer. Med. Ass. *153:* 63, Sept. 5, 1953).

O'Reilly, P.O.; O'Regan, J. B.; Lioanag, E. M.: Triperidol. (A Preliminary Report), Dis. Nerv. Syst. *25:* 221-224, April 1964.

Paulson, G.; Buffaloe, W. J.: Some remarks on the treatment of post-encephalitic oculogyric crises with benztropine methanesulfonate, Int. J. Neuropsychiat. *1:* 214-215, June 1965.

Strang, R. R.: Experiences with COGENTIN in the treatment of parkinsonism, Acta Neurol. Scand. *41:* 413-418, April 1965.

Tanaka, G.; Edwards, J. C.: Treatment of Parkinson's syndrome with tropine benzohydryl ether methane sulfonate and other drugs, J. Gerontol. *7:* 405-409, July 1952.

ISS. 1-95

Manufactured by
Rosemont Pharmaceutical Corporation
Denver, Colorado 80223

Benztropine Mesylate Tablets USP
ANDA 40-103

Rosemont Pharmaceutical Corporation
Attention: Marcy Macdonald
301 S. Cherokee Street
Denver, CO 80223

Dear Ms. Macdonald:

Reference is made to the in vitro dissolution data submitted on December 1, 1994, for Benztropine Mesylate Tablets USP, 0.5 mg, 1 mg and 2 mg.

The Office of Generic Drugs has reviewed the submitted material and has determined that the bioequivalence data is incomplete for the following reason:

> The dissolution testing for the 1.0 mg strength of the test (lot #PD023) and reference (lot #W0804) products was not acceptable and must be repeated according to USP conditions. It is noted that the reference product expiration date is June 1995.

An action described under 21 CFR 314.96 which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290.

In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 16 1995

Benztropine Mesylate
0.5, 1, & 2 mg tablet
ANDA #: 40-103
Reviewer: James D. Henderson
File: 40103W.D94

Rosemont Pharmaceuticals
Denver, CO
Submitted:
December 1, 1994

RESPONSE TO
REVIEW OF A WAIVER REQUEST

Background:

1. On 4/29/94 the sponsor (formerly Pharmaceutical Basics) submitted an ANDA (#40-103) for its test products benztropine mesylate 0.5, 1.0, and 2.0 mg tablets. The listed reference drug is Cogentin® (MSD, NDA #09-193), available as 0.5, 1.0, and 2.0 mg tablets. In support of the request for waiver of *in vivo* study requirements, dissolution data (for both test and reference products) and formulation data (for the test products) were submitted for all three strengths.

2. In response to a telephone request for additional information, the firm submitted an amendment on 6/29/94.

3. The firm was requested by telephone on 8/1/94 to supply dissolution data generated according to USP methods. Since the firm's response was not forthcoming the Division review was completed (file date 11/1/94) and the waiver request was denied.

4. The required data was submitted in a second amendment of 12/1/94.

Comments:

1. The requested dissolution data obtained using the USP method is shown in Table 1. The data is acceptable for the 0.5 and 2.0 mg strengths of the test and reference products.

2. For the 1.0 mg strength of the reference product Cogentin® (MSD lot #W0804), tablet #8 at 5 minutes had only a 9.2 % dissolved. The sponsor attributes this aberrant value to an insufficient amount of 1N sulfuric acid added prior to extraction. According to the sponsor, the release rate values obtained at each of the time points are corrected for the amount of analyte removed from the dissolution vessel at the preceding time point. An incorrect release rate value at the 5-minute time point affects all subsequent values.

Deficiency:

The Division requires acceptable results for dissolution testing using 12 units of the test and reference products. The sponsor acknowledges that dissolution testing results may be uncertain

for the 1.0 mg strength of the reference product. The firm must repeat dissolution testing for the 1.0 mg strength of the test (lot #PD023) and reference (lot #W0804) products according to USP conditions. It is noted that the reference product expiration date is 6/95.

Recommendations:

1. The Division of Bioequivalence does not agree that the information submitted by Rosemont Pharmaceuticals demonstrates that benztropine mesylate tablets 1.0 mg, fall under 21 CFR Section 320.22(d)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the 1.0 mg tablet of the test product is denied.

2. The firm should be informed of the deficiency comment and the recommendation.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK

Concur: Date 2/16/95
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

JDH/crc/2-14-95/40103

cc: ANDA #40-103 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-655 (Patnaik, Henderson), Drug File, Division File

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): benztropine mesylate
Dose Strength: 0.5, 1.0, 2.0 mg tablet
ANDA No.: 40-103
Firm: Rosemont Pharmaceuticals
Submission Date: 12/1/94
File Name: 40103W.D94

I. Dissolution Testing (USP Method):

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.1 N HCl Volume: 900 ml
Specifications: NLT , 30 min
Reference Drug: Cogentin® (MSD)
Assay Methodology: USP

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #PD-022 Strength (mg) 0.5			Reference Product Lot #W0763 exp 6/98 Strength (mg) 0.5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	51.4		7.5	80.2		9.1
10	93.0		3.7	97.1		5.1
15	94.6		3.9	96.9		4.1
20	95.7		4.8	96.1		2.8
30	96.4		5.7	95.9		3.1
45	96.3		6.5	94.9		2.8

Sampling Times (Minutes)	Test Product Lot #PD-023 Strength (mg) 1.0			Reference Product Lot #W0804 exp 6/95 Strength (mg) 1.0		
	Mean %	Range	%CV	Mean %	Range	%CV
5	74.7		11.4	57.7		41.5
10	97.8		3.5	81.6		16.3
15	97.0		3.4	92.2		5.5
20	96.4		3.1	93.8		3.6
30	95.5		4.0	94.5		2.9
45	94.8		2.7	93.0		3.2

Sampling Times (Minutes)	Test Product Lot #PD-024 Strength (mg) 2.0			Reference Product Lot #W0697 exp 4/95 Strength (mg) 2.0		
	Mean %	Range	%CV	Mean %	Range	%CV
5	53.8		18.5	78.1		14.4
10	96.9		3.5	97.3		3.4
15	99.4		1.2	100.1		1.3
20	98.2		1.3	100.1		1.4
30	98.3		1.7	99.8		1.2
45	97.5		1.8	99.6		1.4

DIV

Benztropine Mesylate Tablets USP,
ANDA 40-103

NOV 23 [illegible]

Pharmaceutical Basics, Inc.
Attention: Marcy Huang
301 South Cherokee Street
Denver, CO 80223

Dear Ms. Huang:

Reference is made to the waiver request submitted on April 29, 1994, and the amendment dated June 29, 1994, for Benztropine Mesylate Tablets USP, 0.5 mg, 1 mg and 2 mg.

Reference is also made to the following phone conversations with Jason Gross of the FDA:

August 1, 1994 - Conversation requesting dissolution data.

August 9, 1994 - Conversation with Dr. Waters, discussing the difficulties involved with the September 1, 1994 request.

The Office of Generic Drugs has reviewed the referenced material and we have the following comments:

1. The dissolution methodology submitted to support the approval of this application did not utilize the USP specified methodology. The Office considers the USP methodology as the official method that should be used for *in vitro* dissolution testing.

2. The request for a waiver of *in vivo* bioequivalence testing has been denied. A new waiver request should be included as part of your amendment.

You are required to take an action described under 21 CFR 314.96 which will amend this application.

Representatives of the Division of Bioequivalence are available to discuss this letter and to assist you. Please contact Jason A. Gross, Pharm. D. at (301) 594-0317 for further assistance.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

NOV 1 1994

DIV

Benztropine Mesylate
0.5, 1, & 2 mg tablet
ANDA #: 40-103
Reviewer: James D. Henderson
File: 40103W.494

Pharmaceutical Basics
Denver, CO
Submitted:
April 29, 1994 &
June 29, 1994

REVIEW OF A WAIVER REQUEST

Background:

1) The sponsor has submitted an ANDA (#40-103) for its test products benztropine mesylate 0.5, 1.0, and 2.0 mg tablets. The listed reference drug is Cogentin® (MSD, NDA #09-193), available as 0.5, 1.0, and 2.0 mg tablets. In support of the request for waiver of *in vivo* study requirements, dissolution data (for both test and reference products) and formulation data (for the test products) were submitted for all three strengths.

2) In response to a telephone request (transcript attached) for additional information, the firm submitted an amendment on 6/28/94.

3) The firm was requested by telephone on 8/1/94 (memo attached) to supply dissolution data generated according to USP methods.

Comments:

1. The conditions of use, active ingredient, route of administration, dosage form, and strengths of the test products are the same as those approved previously for the reference products.

2. The sponsor has requested waiver of *in vivo* study requirements in accordance with 21 CFR 320.22(d)(1) of the Bioavailability/Bioequivalence Regulations. The reference product Cogentin® has a therapeutic equivalence rating of "AA" which, for demonstration of bioequivalence, requires only an *in vitro* test.

3. The comparative formulations of the three strengths of the test product are shown in Table 1.

4. The theoretical/finished batch sizes and manufacturing dates were as follows: 0.5 mg, lot #PD-022, 4/28-5/20/93; 1.0 mg, lot #PD-023, 4/28-5/17/93; 2.0 mg, lot #PD-024, 4/28-5/14/93.

5. The results of dissolution testing are shown in Table 2. The assay methodology used by the sponsor was an in-house method which the sponsor states was cross-validated with the USP method (UV 415 nm). Regardless of the acceptability of the in-house method, the firm must submit results of dissolution testing

conducted according to USP conditions, and was so informed on 8/1/94. As of 10/31/94, no data had been submitted.

Deficiency:

The firm must submit results of dissolution testing conducted according to USP conditions, and was so informed on 8/1/94. As of 10/31/94, no data had been submitted.

Recommendations:

1. The Division of Bioequivalence does not agree that the information submitted by Pharmaceutical Basics, Inc., demonstrates that benztropine mesylate tablets 0.5, 1.0, and 2.0 mg, fall under 21 CFR Section 320.22(d)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the 0.5, 1.0, and 2.0 mg tablets of the test product is denied.

2. The firm should be informed of the deficiency comment and the recommendation.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK

Concur: _____ Date 11/1/94
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

JDH/crc/10-31-94/40103

cc: ANDA #40-103 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-655 (Patnaik, Henderson), Drug File, Division File

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): benztropine mesylate
Dose Strength: 0.5, 1.0, 2.0 mg tablet
ANDA No.: 40-103
Firm: Pharmaceutical Basics
Submission Date: 4/29/94
File Name: 40103W.494

I. Dissolution Testing (USP Method):

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.1 N HCl Volume: 900 ml
Specifications: NLT / 30 min
Reference Drug: Cogentin® (MSD)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #PD-022 Strength (mg) 0.5			Reference Product Lot #W0763 exp 6/98 Strength (mg) 0.5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	60.9		7.96	73.0		21.0
10	100.6		1.25	100.5		4.35
15	101.3		1.64	103.2		2.37
20	100.8		1.33	104.1		1.56
30	100.5		1.12	102.9		1.25
45	100.5		1.00	102.2		1.65

Sampling Times (Minutes)	Test Product Lot #PD-023 Strength (mg) 1.0			Reference Product Lot #W0804 exp 6/95 Strength (mg) 1.0		
	Mean %	Range	%CV	Mean %	Range	%CV
5	85.0		4.77	73.7		4.55
10	101.4		3.18	86.0		3.36
15	101.3		3.09	92.0		1.95
20	101.1		3.33	96.0		1.44
30	101.0		3.35	99.2		2.30
45	101.0		3.02	99.1		2.18

Sampling Times (Minutes)	Test Product Lot #PD-024 Strength (mg) 2.0			Reference Product Lot #W0697 exp 4/95 Strength (mg) 2.0		
	Mean %	Range	%CV	Mean %	Range	%CV
5	51.8		10.7	84.3		8.31
10	96.6		4.11	104.1		1.85
15	101.1		2.07	104.4		1.84
20	100.8		1.87	103.7		1.30
30	100.6		2.33	103.1		1.29
45	100.5		2.21	102.7		1.55

ANDA 40-103

DEC 22 1995

Rosemont Pharmaceutical Corporation
Attention: Marcy Macdonald
301 S. Cheokee Street
Denver CO 80223

Dear Madam:

Reference is made to your supplemental new abbreviated drug application dated April 29, 1994, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Benztropine Mesylate Tablets USP, 0.5 mg, 1 mg and 2 mg.

The following comments pertain **only** to bioequivalency issues in the April 29, June 29, December 1, 1994 and June 9, 1995 submissions.

> The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

D.V

DEC 5 1995

Benztropine Mesylate
0.5, 1, & 2 mg tablet
ANDA #: 40-103
Reviewer: James D. Henderson
File: 40103W.695

Rosemont Pharmaceuticals
Denver, CO
Submitted:
June 9, 1995

REVIEW OF AN AMENDMENT

Background:

1. On 4/29/94 the sponsor (formerly Pharmaceutical Basics) submitted an ANDA (#40-103) for its test products benztropine mesylate 0.5, 1.0, and 2.0 mg tablets. The reference listed drug (RLD) is Cogentin® (MSD, NDA #09-193, rated "AA"), available as 0.5, 1.0, and 2.0 mg tablets. In support of the request for waiver of in vivo study requirements, dissolution data (for both test and reference products) and formulation data (for the test products) were submitted for all three strengths.

2. In response to a telephone request for additional information, the firm submitted the first amendment on 6/29/94.

3. The firm was requested by telephone on 8/1/94 to supply dissolution data generated according to USP methods. Since the firm's response was not forthcoming the Division review was completed (file date 11/1/94) and the waiver request was denied.

4. The required data was submitted in a second amendment of 12/1/94. The submission was reviewed (file date 2/16/95) and the waiver request was denied based on unacceptable dissolution testing results for the 1.0 mg strength.

5. The present submission contains the sponsor's response to the deficiency comment from the previous review (file date 2/16/95).

Deficiency Comment:

> **The Division requires acceptable results for dissolution testing using 12 units of the test and reference products. The sponsor acknowledges that dissolution testing results may be uncertain for the 1.0 mg strength of the reference product. The firm must repeat dissolution testing for the 1.0 mg strength of the test (lot #PD023) and reference (lot #W0804) products according to USP conditions. It is noted that the reference product expiration date is 6/95.**

Sponsor's Response: Dissolution data for the 1.0 mg strength of lots PD-023 (Rosemont) and W0804 (MSD) is provided.

Reviewer's Comment: The dissolution testing was performed on 5/22/95 and is shown in Table 1. The sponsor used the USP method. The reported results are acceptable for the 1.0 mg

tablet. It is noted that the sponsor reported CV's as "RNG%" and that the value of "12" was reported for all time points in the row labeled "RSD%". Apparently, the sponsor intended for the values of 12 to reflect the number of units tested, and the values labeled as "RNG%" to be the CV's. The reviewer confirmed these CV values in two cases.

In the previous review (file date 2/16/95) the dissolution data for the 0.5 and 2.0 mg strengths of the test product was found acceptable.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Rosemont Pharmaceuticals demonstrates that benztropine mesylate tablets 0.5, 1.0, and 2.0 mg, fall under 21 CFR Section 320.22 ~~(d)(1)~~ (5) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the 0.5, 1.0, and 2.0 mg tablet of the test product is granted. From the bioequivalence point of view, the test product benztropine mesylate tablets 0.5, 1.0, and 2.0 mg are deemed bioequivalent to Cogentin® tablets manufactured by Merck.

James P Henderson

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK 10/23/95

See Dec 5 7/1 Memo
Concur: ~~Dec 5 66 memo~~ Date 11-1-95
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

JDH/gj/10-16-95/40103

cc: ANDA #40-103 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-655 (Patnaik, Henderson), Drug File, Division File

RD COMPLETED	10/3/95
RD SUBMITTED	10/3/95
RD APPROVED	10/9/95
FINAL SUBMITTED	10/16/95

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): benztropine mesylate
Dose Strength: 1.0 mg tablet
ANDA No.: 40-103
Firm: Rosemont Pharmaceuticals
Submission Date: 6/9/95
File Name: 40103W.695

I. Dissolution Testing (USP Method):

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.1 N HCl Volume: 900 mL
Specifications: NLT / 30 min
Reference Drug: Cogentin® (MSD)
Assay Methodology: USP

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #PD-022 Strength (mg) 1.0			Reference Product Lot #W0804 exp 6/95 Strength (mg) 1.0		
	Mean %	Range	%CV	Mean %	Range	%CV
5	81.0		15.4	75.4		8.9
10	94.1		4.9	98.1		4.8
15	93.2		3.0	97.7		2.2
20	93.4		3.5	96.5		2.2
30	92.2		4.2	97.2		2.2
45	91.1		4.2	97.3		2.4

D.V

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #40-103 SPONSOR: ROSEMONT
DRUG: BENZTROPINE MESYLATE
DOSAGE FORM: TABLET
STRENGTHS/(s): 0.5, 1, AND 2 mg
TYPE OF STUDY: N/A

WAIVER/DISSOLUTION:

Original Submission: 4/29/94
- RLD is Cogentin® (MSD), rated AA; 0.5, 1, and 2 mg tablets
- Sponsor requested waiver of in vivo BE requirements.
- Formulation data submitted for all strengths (qualitatively identical but not quantitatively proportional)
- Dissolution data submitted for all strengths

Amendment #1 submitted 6/29/94 (response to telephone request)
- Result: Sponsor used an in-house method claimed to be cross-validated with the USP method instead of 414 nm).
- Conclusion: Dissolution testing must be repeated with strict adherence to USP conditions.

Amendment #2 submitted 12/1/94
- Dissolution data submitted according to USP method
- Results:
  - Acceptable for 0.5 and 2 mg strengths
  - Aberrant values obtained for one tablet of the 1 mg strength (attributed to experimental error)
- Conclusion: Repeat dissolution testing for the 1 mg strength

Amendment #3 submitted 6/9/95
- Result: Dissolution testing for the 1 mg strength was acceptable.
- Conclusion: Application is acceptable, waiver may be granted under 21 CFR 320.22(c).

PRIMARY REVIEWER: James D. Henderson, Ph.D. BRANCH: II
INITIAL: JH DATE 12-11-95

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D BRANCH: II
INITIAL: RNPatnaik DATE 12/18/95

DIRECTOR, DIVISION OF BIOEQUIVALENCE:
Keith K. Chan, Ph.D
INITIAL: KKC DATE 12/4/95